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Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/750,390
Filing Date: December 31, 2003
Appellant(s): PERRICONE ET AL.

Stephen P. McNamara
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 6/23/09 appealing from the Office action mailed August 20, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

US Patent Applications: 11/344206; 11/34442; and 11/506137.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

20020153509	Lynch	10-2002
4614730	Hansen	9-1986
6294192	Patel	9-2001
6538061	Chaiyawat	3-2003
5985298	Brieva	11-1999

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8 and 11-16 remain/are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitation of: "non-liposome multilamellar crystal non-polar phosphatidylcholine" was not described in the specification as filed, and person skilled in the art would not recognize in the applicant's disclosure a description of the invention as presently claimed. The specification discloses that topical delivery compositions are non-polar in [0010] but not that the phosphatidylcholine is non-polar and that the topical drug delivery compositions may be in liquid crystal phase but not crystal phase [0014]. The Examiner cannot envision how phosphatidylcholine could be non-polar because it is a charged molecule. The Examiner cannot

find a reference to "non-liposome' either. Therefore, it is the Examiner's position that the disclosure does not reasonably convey that the inventor had possession of the subject matter of the amendment at the time of filing of the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 8 and 11-16 remain/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites "non-polar carrier". It is unclear to the Examiner how the carrier can be non-polar if it contains multilamellar *polar* phosphatidylcholine. Claims 2-13 are rejected as being indefinite because they are dependent on an indefinite base claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6, 8 and 11-16 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Amselen et al. (U.S. Patent No. 5,662,932) or Lynch et al. (US 2002/0153509) in view of Hansen et al. (4,614,730) and Patel et al. (U.S. Patent No. 6,294,192) and, with respect to claims 2-6, 8, 15 and 16, Chaiyawat et al. (US 6,538,061) and Brieva et al. (US 5,985,298).

Applicant claims a method of formulating an insulin composition comprising preparing a carrier having a non-liposome multilamellar liquid crystal phosphatidylcholine non-polar carrier.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Amselen et al. teach a method of making a nanoemulsion for administration of a drug comprising preparing a mixture comprising phospholipid and triglyceride (column 14, lines 22-67 and Claim 27). Amselen et al. teach that the core of the particles is solid or liquid crystalline rather than an oil in a fluid phase and can encapsulate medicaments (column 2, lines 43-54).

Amselen et al. teach that the phospholipid can be soy lecithin (phosphotidylcholine) and may be saturated or unsaturated and comprise at least 50% of the total phospholipids (column 6, line 65 through column 7, line 52). (Please note that soy lecithin is enriched with polyenylphosphatidylcholine). Amselen et al. teach that rigid bilayer envelopes are expected thus reading on multilamellar (column 6, lines 56-57 and column 7, lines 39-41). Amselen et al. teach adding nonnatural surfactants such as Tween, SDS and NP-40 (nonylphenylpolyethylene glycol) as well as numerous other synthetic molecules comprise less than 10% (mol/mol) of the total surfactant (Column 7, lines 54-67). Amselen et al. teach that proteins and peptides such as insulin may be present (column 6, lines 21-25). Amselen et al. teach topical administration of the preparation (claim 34). Amselen et al. teach using a homogenizer to mill the composition to ultimately form stable formulations (Column 15, example 1, for example). Amselen et al. teach hydrating the drug-lipid mixture with the aqueous phase utilizing mechanical shaking and homogenizing the resultant dispersion (column 8, lines 58-66 and column 23, example 22, for example). Amselen et al. do not expressly teach that the carrier is non-polar but since the components are the same as instantly claimed, then it is the Examiner's position that it would be non-polar in the absence of evidence to the contrary.

Lynch et al. teach a method of preparing a cubic liquid crystalline active ingredient carrier in claims 17-20. Claim 17 is partially reproduced below:

phase.

17. A method for preparing the cubic liquid crystalline phase precursor of claim 1 comprising the steps of: combining (A) an amphiphile capable of forming a cubic liquid crystalline phase, (B) an optional solvent, (C) an additive selected from the group consisting of an anchor, a tether, and combinations thereof, and (D) an active ingredient, wherein (A), (B), and (C) are present in mass fractions relative to each other such that

Lynch et al. teach that the amphiphile (A) can be phosphatidylcholine ([0050]) and the active (D) can be insulin ([0066]). Lynch et al. teach addition of skin moisturizers thus implying topical skin application ([0066]).

Patel et al. teach a pharmaceutical composition for the topical/transdermal delivery of therapeutic agents comprised of at least one hydrophobic and at least one hydrophilic surfactant as well as solubilizers and mixtures of solubilizers. (Column 25, lines 15-19 and lines 52-53). Polyethylene glycols of average molecular weight of about 200 to about 6000, with PEG-400 a preferred solubilizing agent, are disclosed (Column 25, lines 15-63). Patel et al. disclose that the typical amount of solubilizer present in the composition will be in the range of about 1% to about 100% by weight (Column 26, lines 12-14). Patel et al. teach that hydrophobic surfactants can be in the range of about 1% to about 60% by weight of the hydrophilic surfactant (Column 21, lines 30-31). Patel et al. defines a number of hydrophobic surfactants as oils (Column 9, lines 8-13 and Column 10, lines 1-13; and Table 5, for example). The Examiner is interpreting the addition of such hydrophobic surfactants to mean the addition of a lubricant. Patel et al. further disclose the addition of other additives including preservatives (Column 26, lines 16-21). Methyl paraben is one of the most commonly known preservatives and would be immediately envisaged by one of

ordinary skill in the art. Petal et al. is relied upon for teaching the addition of polyethylene glycols to the composition.

Hansen et al. teach a method of making an insulin composition by dissolving semi-synthetic human insulin in 100 ml of 0.02 N HCl and preparing a carrier comprising dioctanoyl, L-alpha-phosphatidylcholine dissolved in distilled water. The carrier was added to the insulin solution and diluted to 1000 ml with water and produced a product with a stability factor of 65 (Columns 7-8, example 22, for example).

Chaiyawat et al. teach cosmetic compositions comprised of silicone fluids of low viscosity, less than 100 cSt at 25 °C, which exist as fluids at or near room temperature (Column 10, lines 48-59). The lubricious silicone fluids include polydimethylsiloxane polymers (dimethicone) (Column 10, lines 60-67 and Column 11, lines 1-4). Furthermore, Chaiyawat et al. teach that such compositions are suitable as hormone carriers (Column 12, lines 35-38 and 66) as well as drug delivery systems for topical administration of medicinal compositions to the skin (Column 12, lines 55-57). Chaiyawat et al. is relied upon for the teaching of adding polydimethylsiloxane lubricants to the composition.

Brieva et al. teach cosmetic compositions comprised of non-volatile silicones, such as Dow 190 (a surfactant), for improved long lasting adherence to the skin of cosmetics (Column 1, lines 4-42; Column 3, lines 53-65). Brieva et al. is relied upon for teaching the addition of Dow 190 surfactant to the composition.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. Amselen et al. or Lynch et al. do not expressly disclose a method of formulating an insulin composition comprising a phosphatidylcholine component comprising 45% w/w phosphatidylcholine, 50% w/w polyglycol E200 and 5% polyglycol E400.

2. Amselen et al. or Lynch et al. do not expressly disclose a method of formulating an insulin composition comprising 53.25% w/w phosphatidylcholine component, 1.00% w/w siloxylated polyether, 1.00% w/w polydimethylsiloxane, and 0.75% w/w methyl paraben and 44% water.

3. Amselen et al. or Lynch et al. do not expressly teach a method of formulating an insulin composition wherein the insulin is human recombinant insulin prepared in 0.01 N HCl at a concentration of 50 mg/ml or mixing the insulin solution into the carrier for at least one hour and when mixed into said carrier produces an insulin composition having a concentration of 20 mg/ml.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the insulin multilamellar liquid crystalline phosphatidylcholine preparation of Amselen et al. or Lynch et al. with a combination of PEG 200 and PEG 400 as suggested by Patel et al. to produce the instantly claimed invention.

One of ordinary skill in the art would have been motivated to do this because: 1) Amselen et al. and Lynch et al. suggest adding insulin to the multilamellar liquid crystalline carrier and

adding other surfactants; and 2) addition of the low molecular weight PEG would enhance the solubility (Patel et al. Column 25, lines 15-18). The specific w/w ratio of the low molecular weight PEGs to the phosphatidylcholine component in the composition and method of mixing is deemed merely a matter of judicious selection and routine optimization of conventional working conditions taught by Amselen et al. and Patel et al., which is well within the purview of one of ordinary skill in the art as suggested by Patel et al. (Column 26, lines 1-2). "Shaving" appears to be nothing more than adding the phosphatidylcholine to the solvent, in the absence of evidence to the contrary, and would be known to one of ordinary skill in the art. The warming of the components and the choice of 40 C is merely a matter of judicious selection by one of ordinary skill in the art.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of making the carrier composition of Amselen et al. or Lynch et al. to include lubricious silicone fluids, as suggested by Chaiyawat et al., and siloxylated polyethers such DOW 190, as suggested by Brieva et al., and preservatives as suggested by Hansen et al., and produce the instantly claimed invention.

One of ordinary skill in the art would have been motivated to do this because: 1) Amselen et al. and Lynch et al. teach and suggest topical administration to the skin; and 2) Chaiyawat et al. disclose that the addition of such emollients improves the appearance of the skin, reduces flaking and tends to remain on the surface of the skin (Column 10, lines 60-66). Therefore, by adding silicone fluids not only are the aesthetics of the carrier compound improved from a patient standpoint but also the drug delivery capabilities. One of ordinary skill in the art would have been motivated to add DOW 190 because it would have been desirable to increase the

adherence of the drug carrier to the skin for optimal drug delivery (Brieva et al. Column 1, lines 41-42). Hansen et al. teach adding preservatives such as methyl p-hydroxybenzoate (methyl paraben) to the insulin composition, which can be prepared separately and added later to the insulin solution (column 4, lines 11-46). With respect to claims 5, 15 and 16, the selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results (In re Burhans, 69 USPQ 330; CCPA 1946) - see, e.g., MPEP 2144.04 (d).

3. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform a method wherein the insulin is human recombinant insulin prepared in 0.01 N HCl at a concentration of 50 mg/ml or mixing the insulin solution into the carrier for at least one hour and when mixed into said carrier produces an insulin composition having a concentration of 20 mg/ml.

One of ordinary skill in the art would have been motivated to do this because Hansen et al. teaches preparing semi-synthetic human insulin in diluted hydrochloric acid. It is the Examiner's position that semi-synthetic human insulin renders obvious human recombinant insulin to one of ordinary skill in the art. It is the Examiner's position that an acid concentration of 0.01N HCl or an insulin concentration of 50 mg/mL or a final concentration of 20 mg/mL after mixing for at least one hour is merely routine optimization of the composition by one of ordinary skill in the art, in the absence of evidence to the contrary.

Summary: The art teaches preparation of liquid crystalline multilamellar phosphatidylcholine as a carrier for proteins and peptides such as insulin. The art teaches numerous surfactants and lubricants such as polydimethylsiloxane and siloxylated polyethers and solvents/cosolvents such as polyglycols of various molecular weights for use in drug delivery

and cosmetic applications. The order of mixing the ingredients is obvious in the absence of unexpected results.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

1. 35 U.S.C. 112, first paragraph rejection

Appellent asserts that a person of ordinary skill in the art would know that a multilamellar liquid crystal is not a liposome. The Examiner surmises that this is an inherency type argument for support in the specification since the term 'non-liposome' is not verbatim in the specification as filed. However, this is incorrect. Liposomes are inherently/intrinsically multilamellar liquid crystals and Applicant could be making vesicles of some type in the absence of evidence to the contrary.

Appellent also asserts that the carrier is non-polar and not the phosphatidylcholine. This argument has two fatal flaws. If the carrier comprises phosphatidylcholine which is polar, and the drug is entrapped in the phosphatidylcholine of the carrier, then is not the carrier, which is carrying the drug, also polar? One cannot simply make polar phosphatidylcholine non-polar otherwise it would not be phosphatidylcholine. Secondly, when one looks to the specification to see what is meant by "non-polar carrier" you find that is made up of polar polyglycols and adds water [0017-0019] and instant claim 2. Instant claim 2 is directed to a method of preparing the formulation comprises combining ***polar*** polyglycol of MW 200 and ***polar*** polyglycol of MW 400 to form a ***polar*** polyglycol mixture and then ***polar*** phosphatidylcholine is shaved into the ***polar*** polyglycol mixture to form a ***polar*** phosphatidylcholine solution and the ***polar*** solution is mixed until the ***polar*** solution is clear. Applicant's arguments are not persuasive because the 'carrier' is clearly ***polar***.

2. 35 U.S.C. 112, second paragraph rejection

Appellent asserts that claim 1 is definite and that one of ordinary skill in the art will consider the term 'non-polar carrier' to be definite. Respectfully, the Examiner cannot agree. When 'non-polar' describes 'carrier' one of ordinary skill in the art envisions non-polar hydrocarbons and not polar elements such as water or polyglycols and certainly not phosphatidylcholine. It is incongruous to describe a system comprising water, polyglycols and phosphatidylcholine as 'non-polar'. Applicant provided an article (Esposito, AAPS PharmSci 2003) and states that the 'non-polar' carriers of the instant invention are the crystal mesophases described in Esposito. For the record, Esposito is directed to monoglyceride/poloxamer mixtures in water that result in the formation of aqueous dispersions composed of large lipid particles and

nanosomes (Abstract; Figures 1-5; Tables 1-6; and page 13, conclusion). Not only does Esposito *not* make phosphatidylcholine/polyglycol systems but also Esposito appears to support the Examiner's position that liposome like vesicle structures, termed 'nanosomes' by Esposito, are produced upon mixing the ingredients. Appellent's arguments are not persuasive because the carrier is ***polar***.

3. 35 U.S.C. 103(a) rejection

Appellent asserts that the carrier of Amselem is fundamentally different from the loosely arranged multilamellar liquid crystal structure that is instantly claimed. The Examiner cannot agree. First of all, 'loosely arranged' is not a claim limitation. Second of all, in column 13, Table 1, Amselem points out the major differences between a oil-in-water emulsion, a typical liposome and an emulsome. Clearly the invention of Amselem is not a liposome because Amselem distinguishes between these entities.

Appellent asserts that the *phospholipid monolayer is a polar structure* around the lipid core and directs the Examiner to column 6, lines 50-57 reproduced in part below:

> phospholipid monolayer. The number of bilayer envelopes is variable, and may include one, two, or many bilayers. These bilayer envelopes entrap one or more aqueous compartments which may be made to contain a water-soluble drug by creating the lipid particles in the presence of an aqueous solution of that drug.

As shown above, bilayer envelopes are taught and not simply monolayers as asserted by Appellent.

Furthermore, Appellent admits that a phospholipid layer is a polar structure and hence a phospholipid bilayer is polar structure. Since a bilayer is a lamellar structure then a multilamellar

phospholipid structure is polar as well. Applicant has contradicted themselves with respect to their prior arguments concerning multilamellar liquid crystal phosphatidylcholine non-polar carriers. How can the carrier be non-polar when Applicant admits phospholipid layers are polar?

Appellent asserts that Amselem teach neutral lipid core and there is no core lipid present in the instant invention. Respectfully, the Examiner cannot agree because the comprising language of the present invention allows for further ingredients/components including neutral lipid cores.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Appellent asserts that the steps of the method provide a new and unexpected result of a unique multilamellar liquid crystal. However, ***no objective evidence*** to support this assertion has been presented.

Summary: The instant claim language is so contradictory and incongruous with respect to what is known in the art, what has been disclosed by Appellent and what has been argued by Appellent that it is unclear what exactly is being claimed. What is known is that the concept of using phosphatidylcholine to entrap insulin is well known in the art. Appellent has not demonstrated a difference between the art cited by the Examiner and the instant invention but merely argues that they are not the same.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Ernst V Arnold/

Primary Examiner, Art Unit 1616

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